In the Description:

On page 1, after the Title (line 1), ~~on the line~~ inserted prior to the ~~first full~~ paragraph, of the prelim. amdt., insert the heading:

CROSS-REFERENCE TO RELATED APPLICATIONS

On page 1, ~~on the line before the second full paragraph~~ prior to line 4, starting "The present invention relates to", insert the headings:

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BACKGROUND OF THE INVENTION

Field of the Invention

On page 1, ~~on the line before the third full paragraph~~ prior to line 10, starting "It is common", insert the heading:

DESCRIPTION OF THE RELATED ART

On page 1, amend the ~~third and fourth~~ paragraphs starting on line 10 as follows:

It is common prescribing practice for a doctor to prescribe a patient with medicament in a medicament dispenser together with instructions for patient administration of the medicament according to a defined treatment regimen~~regime~~. The patient typically therefore, receives instructions relating to the correct use of the dispenser together with recommended dosing amounts, dose intervals and treatment period. The patient is then trusted to follow the treatment regimen~~regime~~ as set by the doctor.

A limitation associated with this practice is that the treatment regimen~~regime~~ is set at the time of prescription and can therefore not account for changes in the patient's condition over the treatment period. A further limitation associated with this practice is that the onus is on the patient to comply with the doctor's instructions. Occasionally, patients will forget to take the medicament or will vary the treatment regimen~~regime~~ in an unpredictable manner with possible consequences for the success of the treatment.

starting on line 13

On page 2, amend the ~~second full~~ paragraph as follows:

WO99/35588 describes a method for managing the administration of medicine and in particular, monitoring patient compliance with a prescribed treatment regimen~~regime~~. The method relies on input of patient data to a central computer workstation. The central computer workstation calculates and transmits dosage data to a dispensing device via a communications link. The dispensing device delivers drug in accord with the dosage data.

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prior to line 20

On page 2, ~~on the line before the last full paragraph~~ (paragraph starting "The applicants have now developed"), insert the following heading:

BRIEF SUMMARY ON THE INVENTION

starting on line 20

On page 2, amend the ~~last full~~ paragraph as follows:

The Applicants have now developed an improved system for the delivery of medicament which employs an electronic data management system. The system is capable of wireless communication with a network computer system to enable communication of data between the network computer system and the electronic data management system. The system therefore, provides the advantage of enabling data transfer with a network of computers, which network can be made accessible to diverse remote information sources, which may in turn be networked together for cross-transfer of data. The patient therefore, has ready access to diverse, possibly inter-connected, remote information sources capable of providing disease management information. In turn, the system can feed information, such as compliance information, back to any remote information source having access to the network computer system. The system can also be integrated with a healthcare management system for remote prescribing or remote variation or control of the prescribing regimen~~regime~~. The healthcare management system will typically be under the control of a healthcare professional such as a doctor.

prior to line 4,
On Page 12, ~~line 3, before the paragraph starting "Figure 1 is"~~ insert the following heading:

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BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE INVENTION

On page 12, lines 7-24, amend the subject paragraphs as follows:

~~Figure 1.~~ Figure 1 is a schematic representation of a first system in accord with the present invention;

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~~Figure 2.~~ Figure 2 is a schematic representation of a second system in accord with the present invention;

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~~Figures 3. and 4.~~ Figures 3 and 4 are schematic representations of third and fourth systems in accord with the present invention in which the electronic data management system integrates with a system for electronic prescription of medicament;

~~Figure 5.~~ Figure 5 is a system diagram of a ~~third~~ further system in accord with the present invention;

~~Figure 6.~~ Figure 6 is a system diagram of a central controller unit for use in accord with the present invention; and

~~Figure 7.~~ Figure 7 is a system diagram of a patient electronic data manager for use in accord with the present invention.

prior to line 26,
On page 12, ~~line 25, on the line before the paragraph~~ starting "Figure 1. shows" insert the heading:

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DETAILED DESCRIPTION OF THE INVENTION

starting ---, line 26,
Amend the ~~last~~ paragraph on page 12 as follows:

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~~Figure 1.~~ Figure 1 shows a standard-form metered dose inhaler for the delivery of inhalable medicament comprising a tubular housing 10 in which an aerosol

container 12 is located. The housing is open at one end (which will hereinafter be considered to be the top of the device for convenience of description) and is closed at the other. A dispensing outlet 14 leads laterally from the closed end of the housing 10. In the embodiment illustrated, the outlet 14 is in the form of a mouthpiece intended for insertion into the mouth of the patient but it may, if desired, be designed as a nozzle for insertion into the patient's nostril.

On Page 13, amend the ~~first~~ paragraph, starting on line 1, as follows:

The aerosol container 12 is located in the housing 10 so that one end protrudes from the open top of the housing 10. The aerosol container 12 has an outlet valve stem (~~not visible~~see for example, 131 in figure 2) at one end which connects with a support (not shown) in the housing 10. To dispense the dose, the protruding portion of the aerosol container 12 is depressed to move the container 12 relative to the valve stem to open the valve and dispense medicament into the outlet 14 from which it can be inhaled by a patient.

On page 13, in the paragraph starting on line 9, please amend the paragraph as follows:

The dispenser includes an electronic data management system 13 in the form of an integrated circuit preferably integrated into one or more integrated circuit chips and comprised within the housing ~~(not visible)~~. The electronic data management system 13 comprises a memory 16 for storage of data; a microprocessor 17 for performing operations on said data; and a transmitter 18 for transmitting a signal relating to the data or the outcome of an operation on the data. The user may access the electronic data management system by use of push-buttons 20 and toggle menu-button 24. Display 30 allows for display of menu choices and data from the electronic data management system. The dispenser communicates via communications transceiver (also referred to as "communicator") 40 to network computer system 50, through a gateway 52. The network computer system 50 comprises a secure extranet computer system. Remote information sources 60, 62, 63, 64, 66, 68 also have access to the extranet. In more detail, the remote information sources comprise a

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medicament prescriber 60, a pharmacy 62, a weather monitoring station 64, a pollution monitoring station 66 and a medicament manufacturer 68. Other remote information source(s) 63 include, but are not limited to an emergency assistance provider and a research establishment. Two-way data transfer is possible between the electronic data management system and the network computer system 50 via the communications transceiver 40. Information transfer is thus possible between the electronic data management system and any of the remote information sources 60, 62, 63, 64, 66, 68. Information received from any of the remote information sources 60, 62, 63 64, 66, 68 may be utilised by the electronic data management system to vary the recommended medicament dose for delivery to the patient.

On page 13, please amend the paragraph beginning on line 29 as follows:

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~~Figure 2.~~ Figure 2 shows a variation of the system of ~~Figure 2~~Figure 1. The system comprises standard-form metered dose inhaler for the delivery of inhalable medicament comprising tubular housing 110, an aerosol container 112, a valve stem 131, an aerosol valve 134, and dispensing outlet 114. Operation of the inhaler is as described above with reference to Figure 1.

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Insert between lines 7-8 ~~after the first paragraph~~ on page 13, the following two new paragraphs:

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In an alternative form, as alternatively depicted in Figure 2, the system is suitable for the delivery of inhalable medicament and additionally comprises a sensor 132, which senses the breath of a user, wherein the sensor communicates breath data to the electronic data management system. In one aspect, the sensor comprises a breath-movable element which is movable in response to the breath of a patient. More preferably, the breath-movable element is selected from the group consisting of a vane, a sail, a piston and an impeller. In another aspect, the sensor comprises a pressure sensor for sensing the pressure profile associated with the breath of a user. In a further aspect, the sensor comprises an airflow sensor for sensing the airflow profile associated with the breath of a user. In a further aspect, the sensor comprises a temperature sensor for sensing the temperature profile associated with the

breath of a user. The temperature of the inhaled and exhaled part of the breath cycle varies and may, thus, be used as a measurement tool. In a further aspect, the sensor comprises a moisture sensor for sensing the moisture profile associated with the breath of a user. The moisture content of the inhaled and exhaled part of the breath cycle varies and this also may be used as a measurement tool. In a further aspect, the sensor comprises a gas sensor for sensing the oxygen or carbon dioxide profile associated with the breath of a user. The chemical profile of the inhaled and exhaled part of the breath cycle varies and this further may be used as a measurement tool. Suitably, the breath data includes breath cycle data or peak flow data.

Suitably, the system additionally comprises an actuator 133 for actuating the dispensing mechanism, said actuator being actuable in response to a trigger signal from the transmitter. The actuator triggers a mechanism leading to the release of medicament from aerosol valve 134.

On page 14, amend the paragraph beginning on line 8, as follows:

The user accesses the electronic data management system ~~140~~ of the dispenser 110 through the palmtop computer 170. The electronic data management system interacts with the palmtop computer via communicator 140. The palmtop computer 170 itself can communicate through a telecommunications link with network computer system 150, through a gateway 152. The network computer system 150 comprises a secure extranet computer system. As in Figure 1, remote information sources may also have access to the extranet. Two-way data transfer is possible between the electronic data management system and the network computer system 150 via the communications links with the palmtop computer 170. Information transfer is thus possible between the electronic data management system 140, palmtop computer 170 and any of the remote information sources. The system may additionally comprise a geographic positioning system, depicted as optional component 141 (also depicted as 41 in

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Fig. 1), such as a global positioning system or a system which relies on the use of multiple communications signals and a triangulation algorithm.

On page 14, amend the paragraph beginning on line 19 as follows:

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Figure 3 shows a system herein in which patient electronic data management system in dispenser 210 ~~240~~ communicates wirelessly with geographically distant network computer system 250. The network computer system 250 is itself accessible (~~e.~~ i.e., wirelessly or via a modem link) by the system of a medicament prescriber 260 (e.g. a doctor's surgery system) and by the system of a pharmacist 262.

On page 14, please amend the paragraph starting on line 25 as follows:

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The system of Figure 3 may be employed in the remote assessment of a patient and electronic prescribing therefor as follows. The patient data management system in dispenser 210 ~~240~~ communicates data relating to the medical condition of the patient to the network computer system 250. The medicament prescriber 260 accesses this data e.g. ~~by~~ wirelessly by use of a palmtop communications and data management device and makes a judgement as to prescription needs. If a new prescription is needed the prescriber sends a 'prescription authorisation' signal to the network computer system 250. The pharmacist 262 then accesses the network computer system to receive the 'prescription authorisation' signal which authorises them to make up the prescription for the patient.

On page 15, in the paragraph starting on line 1, make the following amendments:

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The system of Figure 4 is a variation of the system of Figure 3 in which patient electronic data management system in dispenser 310~~340~~ communicates wirelessly with geographically distant network computer system 350. The network computer system 350 is itself accessible by the system of a medicament prescriber 360 (e.g. via a modem-enabled personal computer of a doctor). The prescriber system 360 may also access second network computer

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system 354 which is accessible by the system of a pharmacist 362. In an alternative herein, the second computer system 354 may be integral with the system of the pharmacist 362 or be a dedicated secure prescription system accessible only to the prescriber and the pharmacist.

On page 15, in the paragraph beginning on line 11, please amend the specification as follows:

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The system of Figure 4 is employed in the remote assessment of a patient and electronic prescribing therefor as follows. The patient data management system in dispenser 310~~340~~ communicates data relating to the medical condition of the patient to the network computer system 350. The medicament prescriber 360 wirelessly accesses this data and makes a judgement as to prescription needs. If a new prescription is needed the prescriber sends a 'prescription authorisation' signal to the second network computer system 354. The pharmacist 362 then accesses the network computer system to receive the 'prescription authorisation' signal which authorises the pharmacist to make up the prescription for the patient.

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On page 15, please amend the paragraph beginning on line ~~page~~ 22 as follows:

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~~Figure 5.~~ Figure 5 shows a representative system herein comprising an electronic patient data management system in dispenser 410 ~~manager 440 comprised within a drug delivery system (not shown)~~ which would be under the control of the patient. Associated with the patient electronic data management system in dispenser 410~~manager~~ ~~440~~ there is a patient communicator 442 which is capable of wireless communication with a network computer system 450. The system also comprises an authorised user interface 480 having associated authorised user communicator 482 which is capable of communicating with the network computer system 450. Central controller unit 490 is in two-way communication with the network computer system 450.

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On page 15, please amend the paragraph beginning on line ~~page~~ 32 as follows:

The system of ~~Figure 5.~~ Figure 5 is shown in patient 'data upload mode' wherein patient data 444 is wirelessly communicated from the patient data management system ~~manager 440~~ to the network. It may be appreciated that any patient can also communicate requests for data to the network 450 and receive responses thereto via the patient communicator 442 and patient data management system~~manager 440~~. The system is also shown in authorised user 'enquiry mode' in which a database enquiry 484 is communicated to the network computer system 450 and a response received 486 via the authorised user communicator 482 to the authorised user interface 480.

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On Page 16, amend the paragraph beginning on line 7 as follows:

~~Figure 6.~~ Figure 6 shows the structure of the central controller 590 in more detail. The central controller includes a data storage device 591, central processor (CPU) 592, cryptographic processor 593, RAM 594, ROM 595, payment processor 596, operating system 597 and billing processor 598.

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On page 16, amend the paragraph beginning on line 33, as follows:

Figure 7 shows a patient electronic data manager 613~~610~~ comprised with a respiratory drug delivery system ~~(not shown)~~. The electronic data manager 613~~610~~ comprises a central processor unit (CPU) 621; RAM 622; ROM 623 and a cryptographic processor 624. The CPU 621 receives patient data from sensor 615 which may for example be a breath sensor or a sensor detecting actuation of the respiratory drug delivery system. The received data is storable in data storage device 625 which includes two databases, one for storage of patient medical data 626 and one for storage of personal patient data 628. The CPU 621 is associated with man machine interface 620 for receipt of patient input commands and display driver 632 and display 630 for display of information to the patient. The CPU 621 is further associated with communications port 640 which links via wireless communications link 642 to the central controller 690 of a network computer system (not shown).

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On page 17, amend the paragraph beginning on line ~~23~~ 16, as follows:

It will be appreciated that the basic structure of the patient ~~electronic~~ data ~~manager~~ management system 613~~610~~ of Figure 7 can act as an authorised data communicator for making enquiry requests to the databases on the network computer system and receiving responses therefrom. It will also be appreciated that the structure of the patient ~~electronic~~ data ~~manager~~ management system could be adapted by removal of the sensor 615 to form a non-patient authorised data communicator which would not be comprised within a respiratory drug delivery system.

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On Page 17, please amend the paragraph beginning on line 25 as follows:

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Appropriate medicaments may thus be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate (~~eg s~~ e.g., as the sodium salt), ketotifen or nedocromil (~~eg~~ e.g., as the sodium salt); antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone (~~eg~~ e.g., as the dipropionate ester), fluticasone (~~eg~~ e.g., as the propionate ester), flunisolide, budesonide, rofleponide, mometasone ~~eg~~ e.g., as the furoate ester), ciclesonide, triamcinolone (~~eg~~ e.g., as the acetonide) or 6α, 9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydro-furan-3-yl) ester; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol (~~eg~~ e.g., as free base or sulphate), salmeterol (~~eg~~ e.g., as xinafoate), ephedrine, adrenaline, fenoterol (~~eg~~ e.g., as hydrobromide), formoterol (~~eg~~ e.g., as fumarate), isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol (~~eg~~ e.g., as acetate), reproterol (~~eg~~ e.g., as hydrochloride), rimiterol, terbutaline (~~eg~~ e.g., as sulphate), isoetharine, tulobuterol or 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulfonyl]ethyl]amino]ethyl-2(3H)-benzothiazolone;

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adenosine 2a agonists, ~~eg~~ e.g., 2R,3R,4S,5R)-2-[6-Amino-2-(1S-hydroxymethyl-2-phenyl-ethylamino)-purin-9-yl]-5-(2-ethyl-2H-tetrazol-5-yl)-tetrahydro-furan-3,4-diol (~~e.g.~~ e.g., as maleate); α_4 integrin inhibitors ~~eg~~ e.g., (2S)-3-[4-({[4-(aminocarbonyl)-1-piperidinyl]carbonyl}oxy)phenyl]-2-[((2S)-4-methyl-2-{[2-(2-methylphenoxy) acetyl]amino}pentanoyl)amino] propanoic acid (~~e.g~~ e.g., as free acid or potassium salt), diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium (~~eg~~ e.g., as bromide), tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon; vaccines, diagnostics, and gene therapies. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament.

On page 18, please amend the paragraph starting on line 26 as follows:

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Medicaments can also be delivered in combinations. Preferred formulations containing combinations of active ingredients contain salbutamol (e.g., as the free base or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) or formoterol (~~eg~~ e.g., as the fumarate salt) in combination with an anti-inflammatory steroid such as a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate) or budesonide. A particularly preferred combination is a combination of fluticasone propionate and salmeterol, or a salt thereof (particularly the xinafoate salt). A further combination of particular interest is budesonide and formoterol (e.g. as the fumarate salt).